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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/086,477	03/01/2002	Sean C. Semple	INEX.P-006-2	3225

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DORSEY & WHITNEY LLP
555 CALIFORNIA STREET, SUITE 1000
SUITE 1000
SAN FRANCISCO, CA 94104

EXAMINER	
BURKHART, MICHAEL D	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 09/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary	Application No.	Applicant(s)	
	10/086,477	SEMPLE ET AL.	
	Examiner	Art Unit	
	Michael D. Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-12 and 14-19* is/are pending in the application.

4a) Of the above claim(s) *4 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 5-12, 14, and 16-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/30/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 6/30/2006 has been entered.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, Application Nos. 09/078,954 and 08/856,374, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. There are no teachings of

sequences with a CpG motif in either 09/078,954 or 08/856,374. The earliest teaching of such motifs in the claimed priority chain is found in the 60/151,211 application. The instant invention is thus granted a priority date of 8/27/1999, the filing date of the '211 application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11, 12, 14 and 16-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 recites the limitation "the target antigen" in line 3. There is insufficient antecedent basis for this limitation in the claim. This rejection affects all dependent claims.

Claim 19 recites the limitation "the exchangeable steric barrier" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim. Claim 19 should depend from claim 18, and has been treated as such for examination purposes below.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this

subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 5, 9-12, 14, and 16 are rejected under 35 USC 102(e) as being anticipated by Krieg et al (US 6,207,646, of record).

Krieg et al teach that cationic lipid or liposome carriers (column 12, lines 25-34) can be employed to encapsulate a CpG motif as an immunostimulatory nucleic acid complex along with an antigen, which may be encoded by DNA (claims 14, 16, 18, 24, etc.). Absent evidence to the contrary, the antigen/DNA is also considered a drug.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 5-12, 14, and 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al (US 6,207,646, of record) in view of Wheeler et al (US 5,981,501, 1999, of record), Gokhale et al (Gene Ther. 1997), or Hope et al (Mol. Memb. Biol., 1998, cited by applicants).

The teachings of Krieg et al are as above and applied as before. Krieg et al do not teach the use of a specific cationic lipid selected from those listed in claims 6 and 17, nor the use of a steric barrier lipid, as recited in claims 7 and 8, for example.

Hope et al demonstrates the encapsulation of DNA by lipids in a DODAC-DOPE-DNA complex (see in particular Fig. 7A), and that such techniques for encapsulation of DNA by lipids were commonly used in the art at the time of, and prior to, Krieg et al (see, for example, first and second columns, page 1). There were no apparent strands of sheathed DNA projecting from the particles (page 8, first column, first full ¶). Hope et al also teaches that DNA is protected from nuclease degradation when complexed with lipids, and that such protection is critical for *in vivo* gene therapy using an oligonucleotide (page 8, first column, second full ¶).

Wheeler et al also teach the encapsulation of DNA within lipid particles, see in particular Fig. 3 and the ¶ linking columns 1 and 2. Wheeler et al specifically teach the use of DODAC, DOTMA, DOTAP, etc. in column 5, lines 19-31, and the use of PEG-lipids and gangliosides in column 11, lines 41-48. Wheeler et al teach that the encapsulation of DNA by the lipid particles of their invention prevents degradation of DNA by nucleases and allows the production of serum-stable particles suitable for *in vivo* use (column 6 and abstract).

Gokhale et al also teach the encapsulation of oligonucleotides within lipid particles, see in particular Fig. 1 and the ¶ linking the first and second columns, page 1290. Gokhale et al specifically teach the use of DDAB and DOTAP in the ¶ linking pages 1289 and 1290. Gokhale et al teach that the encapsulation of DNA by the lipid particles of their invention prevents degradation of the oligonucloetides by plasma following *in vivo* administration (¶ linking pages 1290-1291) and allows the production of liposome-encapsulated oligonucleotides suitable for *in vivo* use (abstract, page 1289, second column, first full ¶).

The claimed compositions comprising a CpG oligodeoxynucleotide fully encapsulated in a lipid particle comprising a cationic lipid is disclosed by Krieg et al with the exception of the

specific cationic lipids and steric barrier lipids recited, for example, in claims 6-8. The ordinary skilled artisan, seeking a stable lipid particle for *in vivo* delivery of the CpG oligonucleotides taught by Kreig et al, would have been motivated to use the cationic lipids and steric barrier lipids of Hope et al, Wheeler et al, and Gokhale et al because all of the previous references teach the use of these lipids in preparing lipid-DNA particles that are stable and serum-resistant. It would have been obvious for the skilled artisan to do this because of the known benefit of generating lipid-DNA particles that are not degraded by serum nucleases as taught by Hope et al, Wheeler et al, and Gokhale et al. Given the teachings of the cited references and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered, absent evidence to the contrary, that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Response to Arguments

Applicant's arguments filed 6/30/2006 have been fully considered but they are not persuasive. Applicants' arguments are directed to USC 103 rejections using a different set of references, although some of the references used are in common (i.e. Wheeler and Krieg). To the extent that the arguments are relevant to the instant USC 103 rejection, they are addressed below. Applicants essentially assert that: 1) no motivation to combine the references is found within the references themselves, that Krieg in particular only mentions lipid encapsulation "in passing" and that Wheeler et al is not directed to immunostimulatory compositions, but rather to antisense or gene therapy; 2) Wheeler et al teaches away from immunostimulatory compositions, teaching the use of sequence-specific nucleic acids for gene therapy and the reduction of any unwanted immune response(s); 3) the Examiners reliance upon "the totality of the prior art" is

erroneous and simplistic, and that applicants selection of a particular lipid vehicle is non-obvious; 4) the teachings of Krieg et al to encapsulate their compositions within liposomes/cationic lipids is an invitation to experiment or "obvious-to-try" situation; 5) Dow et al teach away from encapsulating nucleic acids within liposomes, rather, Dow et al teach the formation of DNA/lipid "complexes", and that such complexes are taught by Zelphati et al to be sufficient for protection from serum nucleases; 6) there was no reasonable expectation of success for the lipid/DNA compositions of the prior art, as evidenced by Zelphati et al and Hope et al; 7) the mechanism/site of action for CpG oligonucleotides was unknown at the time of the invention; 8) applicants demonstration of unexpected and superior results (i.e. the Hope declaration) rebuts the contention of obviousness.

Regarding 1), the motivation to combine the references, i.e. to produce a stable lipid/DNA particle useful for *in vivo* administration, is clearly expressed in the above rejection and is taught by Hope et al, Wheeler et al, and Gokhale et al. Regarding 1) and 2), in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Further regarding 2) and regarding 7), the teachings of Wheeler et al regarding gene therapy and the undesirability of an immune response is moot in light of the teachings of Krieg et al, the object of Krieg et al (the primary reference of the rejection) is to create an immune response. As such, the skilled artisan would recognize that in order to be efficacious, the lipid/DNA particles must reach their intended target, i.e. target cells. Furthermore, it is unclear how the mechanism of CpG activation is relevant to the instant

rejection. This is because one of skill in the art would understand that the CpG oligonucleotides of Krieg et al would have to reach the target cell in order to be efficacious, regardless of the mechanism of action. Regarding 3), the totality of the prior art is the standard for USC 103 rejections. It is unclear what applicant believes is erroneous or simplistic about the application of prior art that teaches the claim limitations. The instant claims are not limited to a "particular" lipid, hence it is unclear what applicants are referring to in this regard. Regarding 4), the teachings of the prior art are the opposite of "obvious-to-try" or an invitation to experiment. Each of Hope et al, Wheeler et al, and Gokhale et al teach specific cationic lipid/DNA compositions and how to prepare them using commonly available reagents. Regarding 5), given the teachings of Hope et al, Wheeler et al, and Gokhale et al, it is reasonable that the lipid/DNA complexes of Dow et al (using DOTAP and cholesterol) represent encapsulated DNA, hence the observed serum protection. This is additionally supported by Zelphati et al who, on page 34, first ¶, state:

> " However, degradation of phosphodiester oligonucleotides by nucleases was markedly prevented by DOTAP both in cell culture medium and in human serum (12, 13). This can be explained by a collapse or a "coating" of the oligonucleotides after aggregation of the complexes, leading to structures where the oligonucleotides are completely covered by lipid bilayers."

Regarding 6) and 8), given the success of the lipid/DNA compositions taught by Hope et al, Wheeler et al, and Gokhale et al, it is unclear to the Examiner what teachings in these references could be construed as an "unreasonable expectation of success" and "unexpected" results. Further regarding 8), the teachings of Hope et al, Wheeler et al, and Gokhale et al do not disclose the use of CpG oligonucleotides, let alone the use of the specific CpG nucleotide, cells, and

assay found in the Hope declaration. Therefore, a comparison between the teachings of Hope et al, Wheeler et al, and Gokhale et al and those of the Hope declaration is not possible. Applicants allegation of superior results is thus unsupported and not convincing. Applicants comparison with the Dow reference is also flawed, as Dow did not use an oligonucleotide as in the Hope declaration, but rather a plasmid, and Dow used DOTAP/cholesterol rather than DODAC/DOPE or DSPC/CH/DODAP/Peg-Cer-C14, as in the Hope declaration.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 5-12, 14, and 16-19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-6, 9, 10 and 23 of copending Application No. 10/290,545. Although the conflicting claims are not identical, they

are not patentably distinct from each other because the instantly claimed compositions are used in the methods of the '545 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The '545 application claims recite a method for stimulating an enhanced immune response in a mammal by administering, to the mammal an immunostimulatory composition comprising a lipid-nucleic acid formulation associated with at least one antigen, wherein the nucleic acid is fully encapsulated (claim 1). The lipid component comprises a cationic lipid (claim 4) and a neutral lipid (claim 5), the oligonucleotide is oligodeoxynucleotide that comprises at least one CpG motif (claims 9 and 10). The specification discloses that the immunostimulatory composition can be used either alone as an adjuvant or associated with an antigen in a vaccine (p. 9, paragraph 0145), can be used to modulate the levels of cytokines (p. 17, paragraph 0217), and that the composition can further comprise drugs or bioactive agents (p. 15, paragraph 0197). With respect to the limitation of a PEG-lipid, the specification discloses that the composition can further comprise PEG-lipids (p. 12, paragraph 0168) and PEG-DMG is recited in claims 6 and 23 of '545.

Claims 1, 3, 5-12, 14, and 16-19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 20, 21, 23, 26, 27, 29, 30, 34, and 39 of copending Application No. 10/788,028. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed compositions are used in the methods of the '028 application.

The '028 application claims recite a method for stimulating cytokine secretion or an immune response in a mammal by administering compositions comprising a nucleic acid fully encapsulated within a lipid particle comprising a cationic lipid (claims 20 and 21) and an antigen, which may be a nucleic acid encoding the antigen (claim 21). The cationic lipid component may be any of those recited in claim 26 or 27. The nucleic acid may comprise at least one CpG motif (claims 23 and 34). With respect to the limitation of a PEG-lipid, these are recited in claims 29 and 39. The methods may use a composition further comprising a drug or cytotoxic agent (claims 30).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Burkhart whose telephone number is (571) 272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael D. Burkhart
Examiner
Art Unit 1633

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER